PB88-162433

Health and Environmental Effects Profile for Folpet

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-162433

EPA/600/X-84/327
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR FOLPET

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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-84/327	2.
3. RECIPIENT'S ACCESSION NO. PB88 162439/AS	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Folpet	5. REPORT DATE January 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Same as box 12.	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Health and Environmental Effects Profile for folpet was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Folpet has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for folpet is 5×10^{-3} (mg/kg bw/day)$^{-1}$ for oral exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 58
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	4
2.1.	WATER	4
2.2.	AIR	5
2.3.	SOIL	6
3.	EXPOSURE	7
3.1.	WATER	7
3.2.	FOOD	7
3.3.	INHALATION	9
3.4.	DERMAL	9
4.	PHARMACOKINETICS	10
4.1.	ABSORPTION	10
4.2.	DISTRIBUTION	10
4.3.	METABOLISM	11
4.4.	EXCRETION	11
5.	EFFECTS	12
5.1.	CARCINOGENICITY	12
5.2.	MUTAGENICITY	12
5.3.	TERATOGENICITY	20
5.4.	OTHER REPRODUCTIVE EFFECTS	25
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	25
5.6.	OTHER RELEVANT INFORMATION	26
6.	AQUATIC TOXICITY	27
6.1.	ACUTE	27
6.2.	CHRONIC	27
6.3.	PLANT EFFECTS	30
6.4.	RESIDUE	30
6.5.	OTHER RELEVANT INFORMATION	30

Page

7. EXISTING GUIDELINES AND STANDARDS 31

7.1. HUMAN. 31
7.2. AQUATIC. 31

8. RISK ASSESSMENT 32

9. REFERENCES. 35

APPENDIX: LITERATURE SEARCHED. 47

LIST OF TABLES

No.	Title	Page
3-1	Summary of Folpet Analysis in Domestic Large and Small Fruit for Fiscal Years 1970-1976.	8
5-1	Carcinogenicity of Folpet	13
5-2	Mutagenicity of Folpet.	14
5-3	Teratogenicity of Folpet.	22
6-1	Acute Toxicity of Folpet to Aquatic Organisms	28

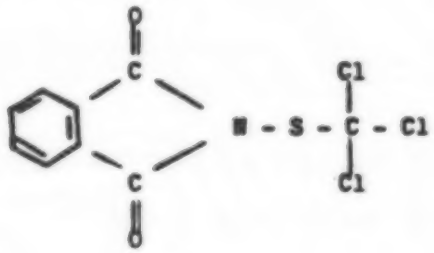
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
LOAEL	Lowest-observed-adverse-effect level
MTD	Maximum tolerable dose
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
SGOT	Serum glutamic oxalacetic transaminase
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Folpet is the common name for N-(trichloromethanesulfenyl)phthalimide. Current Chemical Abstract usage is 2-[(trichloromethyl)thio]-1H-isoindole-1,3(2H)-dione and was formerly N-(trichloromethylthio)phthalimide (Martin and Worthing, 1977). It was introduced in 1949 by the Standard Oil Development Co., and later by the Chevron Chemical Co. under the trademark "Phaltan" (Martin and Worthing, 1977). Other trade names include Orthophaltan, Phthalan, Spolacid, Faltan, Folpan, Folpet and Thiophal. The stuctural and empirical formulae for folpet are as follows:



Empirical formula: $C_9H_4Cl_3NO_2S$

Molecular weight: 296.6

The Chemical Abstract Services (CAS) Registry number is 133-07-3.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

Folpet is a white crystalline solid when pure (Spencer, 1968); the technical product is ~90% pure (Martin and Worthing, 1977). Selected physical properties are listed below:

Melting point:	177°C (Martin and Worthing, 1977)
Vapor pressure:	$<10^{-5}$ mm Hg at 20°C (Martin and Worthing, 1977)
Water solubility:	1 mg/ℓ at room temperature (Martin and Worthing, 1977)

Log octanol/water partition coefficient:	3.63 (Briggs, 1981)
BCF:	618 (Kenaga, 1980) (calculated from water solubility)
Soil sorption coefficient: (calculated from water solubility)	4400 (Kenaga, 1980)

Folpet is only slightly soluble in organic solvents. It is stable when dry, but slowly hydrolyzes in water at ambient temperatures. The hydrolysis becomes rapid at high temperatures or under alkaline conditions. Folpet is incompatible with alkaline pesticides and is noncorrosive, although its decomposition products are corrosive. It is virtually nonvolatile (Spencer, 1968; Martin and Worthing, 1977).

1.3. PRODUCTION DATA

Folpet is manufactured by the reaction of trichloromethylsulphenyl chloride (perchloromethyl mercaptan) with sodium phthalimide (Martin and Worthing, 1977; Spencer, 1968).

The domestic manufacturers of folpet are Standard Oil of California (Chevron Chemical, Ortho Div.) and Stauffer Chemical (Calhio Chemical) in Perry, Ohio, (SRI, 1983; USITC, 1983a) in a joint venture (SRI, 1976). Current production figures for folpet are not available. In 1982, nearly 110,000 pounds of folpet were imported into the United States (USITC, 1983b).

1.4. USE DATA

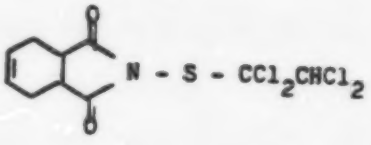
Folpet is a protective fungicide used mainly for foliage application, and is especially useful for control of grape diseases (Martin and Worthing, 1977). Application rates are reported to be 100 g active ingredient/100 ℓ (Martin and Worthing, 1977) and 2 lb/100 U.S. gal (Spencer, 1968).

During 1975, consumption of folpet in the United States was estimated to be 1.8 million pounds with use on apples, citrus fruits, deciduous fruits, vegetables, and paints and wood preservatives estimated to be 0.2, 0.3, 0.2, 0.4 and 0.7 million pounds, respectively (SRI, 1976). Use of folpet on grapes in New York and Pennsylvania in 1979 was 56,000 pounds (Fluke et al., 1982).

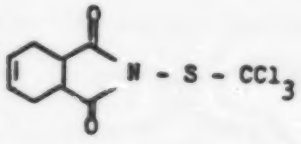
2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

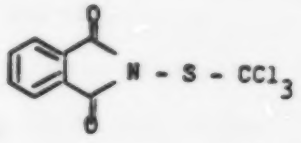
Like other chemicals, the fate of folpet in water will depend on its ability to undergo chemical, photochemical and biological reactions, and its partitioning between sediments and the atmosphere. Wolfe et al. (1976a) suggested that hydrolysis is likely to be the predominant pathway of degradation of folpet in the aquatic environment due to its rapid degradation rate in water. Using a buffered pH range (7.0-7.2), Wolfe et al. (1976a) found that degradation half-lives of the fungicides captafol, captan and folpet followed apparent first-order reaction kinetics with rate constants at 28°C of $7.7 \times 10^{-5} s^{-1}$, $6.5 \times 10^{-5} s^{-1}$ and $1.4 \times 10^{-4} s^{-1}$, respectively. The chemical structures of these fungicides (as shown below) suggest a similar hydrolysis mechanism.



Captafol



Captan



Folpet

The hydrolysis half-lives of captafol, captan and folpet, using the apparent-first-order rate constants above, are 150, 178 and 83 minutes, respectively. The same experiment was conducted with natural water from the Tombigbee River in South Carolina (pH = 7.0) for captan; the calculated half-life was 155 minutes, which is in good agreement with the previously calculated 170 minutes. Additionally, Wolfe et al. (1976a) measured the hydrolysis rate of captan over the pH range 2-9. From pH 2-6, the hydrolysis half-life was ~11 hours, but decreased rapidly thereafter until a half-life of 10 minutes was reached near pH 9. The pH-hydrolysis profile for folpet may be similar, although this has not been investigated.

The photodegradation of folpet has not been comprehensively studied. Gore et al. (1971) determined the UV spectra of folpet, which shows no absorption at >300 nm and very little absorption between 290 and 300 nm. This would indicate that direct photolysis of folpet is not environmentally significant; however, it may be possible that the photosensitized decomposition of folpet has greater significance. Wolfe et al. (1976b) found that the photosensitized oxygenation of the structurally similar fungicide, captan, may have some importance concerning environmental loss, although not as significant as hydrolysis decomposition. Serra (1964) reported that the degradation of a thin film of folpet exposed to sunlight irradiation was less than that of captan or captafol; 51% of the captan had degraded after 3 days.

Data specific to the microbial degradation of folpet in aquatic media were not located in the available literature cited in the Appendix.

The transport of folpet via sedimentation or volatilization from water has not been studied. Data discussed in Section 2.3. predict that folpet may be tightly sorbed in soils; therefore, sorption by particulate matter present in water may be possible.

Kenaga (1980) has predicted a BCF based upon water solubility for folpet of 618, which indicates that folpet may not be strongly bioconcentrated. However, the measured log octanol/water partition coefficient of 3.63 (Briggs, 1981) indicates that folpet may be strongly bioconcentrated. Experimentally determined BCFs are not available from the literature in the cited Appendix.

2.2. AIR

Data specific to the fate and transport of captafol in the air were not located in the available literature in the cited Appendix. The UV spectra

of folpet, as determined by Gore et al. (1971) (see Section 2.1.), would indicate that direct photolysis in the atmosphere is not likely to be significant.

2.3. SOIL

The fate and transport of folpet in the soil has received very little study. As noted in Section 2.1., folpet undergoes rapid hydrolysis in water; therefore, folpet may hydrolyze significantly in moist soils.

Wolfe et al. (1976b) suggested that the sensitized photooxidation of captan on leaf, fruit or soil surfaces may have some importance. Photodegradation of folpet from soil surfaces may therefore be possible, although this mechanism has not been investigated. However, photodegradation likely plays a minor role in relation to hydrolysis.

Data specific to the microbial degradation of folpet in soils were not located in the literature cited in the Appendix.

Kenaga (1980) has predicted the soil sorption coefficient (K_{oc}) for folpet, based upon its water solubility, to be 4400. Compounds having a K_{oc} value of $\geq$1000 are tightly bound to organic matter in soil and are considered immobile (Kenaga, 1980). The log octanol/water partition coefficient of 3.63 (Briggs, 1981) predicts that substantial sorption may occur in soil, as does the experimentally measured log soil sorption coefficient (K_{oc}) of 3.03 (Briggs, 1981).

Volatilization from soil can be inversely related to soil sorption. As noted above, soil sorption is probably high; therefore, folpet volatilization from soil may be very low.

The overall persistence of folpet in soil is not available; Neely (1970) field-tested the persitence of folpet on 12 types of wood and leaves during a dry summer in Illinois and found an average persistence of 1.8 weeks.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base (see Appendix) contains no monitoring data for folpet. Data regarding exposure of folpet in water in the United States were not located in the literature cited in the Appendix. An abstract of a foreign study reports that folpet concentrations, in waste waters from a sugar beet factory in which the stored beets were fumigated with folpet 40-45 days previously, were 0.025-0.05 mg/ℓ (Cerna and Benes, 1977).

3.2. FOOD

McLeod et al. (1980) monitored Canadian food in a national survey to determine pesticide residues in the total diet. Food samples were collected from five Canadian regions representing 11 classes of food. Monitoring for folpet was done with a minimum detection limit of 5 ppb; no folpet was detected.

The U.S. Food and Drug Administration has monitored American foods for pesticide residues during the Total Diet Program and the FDA Monitoring Program. The Total Diet Program analyzed ready-to-eat food composites obtained from ~30 cities annually, while the Monitoring Program examined raw agricultural commodities, both domestic and imported. During the fiscal years 1970-1976, 808 samples of imported large fruits and 1089 samples of imported small fruits were analyzed for residues of folpet; no folpet residues were detected (Duggan et al., 1983). Analysis of domestic large and small fruits is tabulated in Table 3-1 for the fiscal years 1970-1976.

In addition, folpet was infrequently found in vegetable leaves and stems during 1970-1976, with only two positive detections (Duggan et al., 1983).

TABLE 3-1

Summary of Folpet Analysis in Domestic Large and Small Fruit
for Fiscal Years 1970-1976*

	Large Fruit	Small Fruit
Number samples analyzed	3212	1201
Number samples with:		
No detection	3170	1188
Trace-0.03 ppm	5	1
0.04-0.10 ppm	15	3
0.11-0.50 ppm	18	7
0.51-1.00 ppm	3	2
1.01-1.50 ppm	0	0
1.51-2.00 ppm	0	0
>2.00 ppm	1	0

*Source: Duggan et al., 1983

In abstracts from foreign studies, Bencivenga et al. (1980) detected folpet and other pesticides in very small amounts (trace-1.80 ppm) in table grapes grown near Rome, Italy. Gambettiova and Kovac (1974) detected folpet in grape juice made from grapes sprayed with folpet, and noted that the folpet persisted in the juice for 18 days. Cerutti et al. (1981) examined 132 wines (produced in Italy) for pesticides and detected folpet (1 ng/ml) in one wine. Polizu et al. (1973) detected folpet on grapes treated with the fungicide at levels of 1.5-11.0 ppm, depending upon the interval between application and examination. They also detected folpet residues of 0.0-0.8 ppm in year-old wines. Andersson and Josefsson (1981) found folpet residues in one of 55 samples of lettuce in Sweden. Cerna and Benes (1977) detected folpet levels of 0.006-0.051 mg/kg and 0.013-0.06 mg/kg on the surface of and within sugar beets, respectively, 40-45 days after the sugar beets were fumigated with folpet and remained in storage.

3.3. INHALATION

Pertinent data regarding inhalation exposure to folpet were not located in the literature cited in the Appendix.

3.4. DERMAL

Pertinent data regarding dermal exposure to folpet were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of folpet were not located in the available literature. However, folpet appeared to be absorbed much more efficiently when administered intraperitoneally than when administered orally, as evidenced by alterations of SGOT levels in male rats given an intraperitoneal dose of 50 mg of folpet/kg bw. An oral dose of 500 mg/kg of folpet did not affect the SGOT level in rats (Ashley et al., 1982).

4.2. DISTRIBUTION

Six male Sprague-Dawley rats received a single intraperitoneal injection of 6 mg/kg of [^{14}C]-folpet (Couch et al., 1977). The location of the radioactive carbon was not disclosed, but the discussion implied that it was located in one of the ring carbons. Three animals were killed 24 hours after treatment; the rest, 72 hours after treatment. In multiple dose experiments, three Sprague-Dawley rats received a 6 mg/kg intraperitoneal injection of folpet at 0, 24 and 48 hours. Twenty-four hours after the last injection, the animals were killed (Couch et al., 1977). In the single dose experiment 24 hours after dosing, a relatively high concentration of Folpet and metabolites (0.51$\pm$0.53 µg of [^{14}C] folpet equivalents/g of tissue, wet weight) occurred in the kidneys, followed by the lungs (0.45$\pm$0.34 µg/g), liver (0.33$\pm$0.30 µg/g) and plasma (0.24$\pm$0.04 µg/g) 0.04 µg/g). By 72 hours after dosing, the highest concentration of folpet equivalents occurred in the whole blood (0.31$\pm$0.40 µg/g) followed by the plasma (0.24$\pm$0.50 µg/g), kidneys (0.23$\pm$0.18 µg/g), lung (0.20 µg/g), spleen (0.14$\pm$0.21 µg/g) and liver (0.11$\pm$0.19 µg/g). Although the concentration of folpet equivalents was very high (0.85$\pm$0.12 µg/g) in muscle 24 hours after dosing, it became quite low (0.02$\pm$0.01 µg/g) within

72 hours of dosing. In the multiple dose experiment, the highest concentration of folpet equivalents occurred in the plasma (0.40±0.16 µg/g) followed by whole blood (0.35±0.14 µg/g), lungs (0.22±0.07 µg/g), kidneys (0.20±0.04 µg/g), spleen (0.14±0.03 µg/g), fat (0.14±0.05 µg/g) and liver (0.13±0.05 µg/g). The authors stated that the phthalimide moiety, one of the breakdown products of folpet, did not accumulate in the tissues (Couch et al., 1977).

4.3. METABOLISM

Folpet reacts chemically with the thiol group of glutathione to produce thiophosgene ($Cl_2C=S$), phthalimide and the corresponding disulfide (Davidek and Seifert, 1975). Folpet was inactivated (decrease in mutagenic potential) by sulfhydryl groups in the blood and on cysteine, as well as by the rat liver homogenate S-9 mixture (Moriya et al., 1978).

4.4. EXCRETION

Nine male Sprague-Dawley rats received a single intraperitoneal injection of 6 mg/kg of [^{14}C]-folpet. The position of the radioactive carbon was not indicated. After 24 hours, 103.0±2.2% of the label appeared in the urine, 1.7±1.6% in the feces; during the next 24-hour period, 1.3±0.2% in the urine, 0.9±0.6% in the feces; while during the last 24-hour period of this 72-hour study, 0.6±0.5% in the urine, 0.3±0.3% in the feces. In a multiple exposure experiment, six male Sprague-Dawley rats received an intraperitoneal injection of 6 mg/kg of folpet at 0, 24 and 48 hours. Urine was collected at 0, 24 and 48 hours. At 24 hours, 102.6±3.5% of the label appeared in the urine, 2.8±2.2% in the feces; at 48 hours, 100.6±4.7% of the label administered at 24 hours appeared in the urine, 3.8±2.2% in the feces; and at 72 hours, 100.6±0.6% of the label administered at 48 hours appeared in the urine, 4.6±1.1% in the feces (Couch et al., 1977).

5. EFFECTS

5.1. CARCINOGENICITY

In an NCI study summarized by Innes et al. (1969) and described more fully in data reports submitted by Bionetics Research Laboratories (BRL, 1968), 18 male and 18 female mice from the B6C3F1 strain and 18 male and 18 female from the B6AFK1 strain were given 215 mg/kg/day of folpet by intubation beginning on day 7. The vehicle was 0.5% gelatin, and the daily dose of folpet (experimentally determined to be the MTD) was not adjusted for growth-associated weight gain. After weaning at 4 weeks of age, the mice received folpet mixed directly with the diet at a concentration of 603 ppm. The mice were killed at 18 months. The incidence of tumors in the mice continuously exposed to folpet was not significantly higher than in the controls (Innes et al., 1969) (Table 5-1).

5.2. MUTAGENICITY

Several abstracts reported that folpet was mutagenic in microbial systems (Rideg, 1982; Jorgenson et al., 1976; Nagy et al., 1975; Simmon et al., 1976, 1977). Table 5-2 summarizes these mutagenicity studies. McCann et al. (1975) found folpet to be mutagenic, but did not use S-9 in the assay. Moriya et al. (1978) reported that folpet was inactivated by S-9, cysteine and blood. Although Simmon et al. (1977) reported using a mammalian activation system in their assay, other studies that incorporated S-9 into the assay have not found folpet to be mutagenic (Rosenkranz and Leifer, 1980; Moriya et al., 1983; Shiau et al., 1981). The results of the studies by Shirasu et al. (1976), Kada et al. (1980) and Moriya et al. (1983) indicated that folpet caused a base-change rather than a frameshift mutation.

TABLE 5-1

Carcinogenicity of Folpet[a]

Route	Strain	Number of Mice[b]		Total Number of Mice with Tumors[b]	
		M	F	M	F
NA (negative control group)	B6C3F1	73	83	22	8
	B6AKF1	89	75	16	7
Oral	B6C3F1	18	17	5	2
	B6AKF1	16	13	2	1

[a]Source: BRL, 1968

[b]The number of mice per group that were sacrificed at the terminal kill after 18 months of oral folpet administration.

TABLE 5-2

Mutagenicity of Folpet

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium	TA1535, TA1536, TA1536, TA1537, TA1538, TA98, TA100	50, 100 or 300 g/disc	spot test	+/-	-/-	Authors reported what appeared to be total increases in colony count rather than the presence or absence of a ring of revertant colonies.	Shiau et al., 1981
Reverse mutation	S. typhimurium	TA100	1-300 µg/plate	liquid incubation assay	-	-	Incubation took place for 30 minutes prior to plating.	Shiau et al., 1981
Reverse mutation	S. typhimurium	TA100, TA1535	64 mmol	NR	-	+	The authors did not describe strain-specific results.	McCann et al., 1975
Reverse mutation	S. typhimurium	his646 TA1530 TA1531 TA1532 TA1534	NR	NR	NR	+ + - - -	NC	Sofler, 1973
Reverse mutation	S. typhimurium	TA1535 TA1536 TA1537 TA1538	100 µg/plate	plate incorporation	NR	+ - - -	NC	Shirasu et al., 1976; Kada et al., 1974, 1980
Reverse mutation	S. typhimurium	TA1535, TA100, TA1537, TA1538, TA98	5-500 µg/plate	plate incorporation	+/-	+	Although data were not given for each experiment, folpet was mutagenic at lower dose levels in the absence of S-9 in the TA100 strain.	Moriya et al., 1983
Reverse mutation	S. typhimurium	TA1535, TA1537, TA1538, TA98, TA100	<10 mg/plate	plate incorporation	+/-	+	Responses were not reported individually for each strain, or for the presence or absence of S-9.	Waters et al., 1982

TABLE 5-2 (cont.)

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Reverse mutation	Bacillus subtilis	TKJ5211, TKJ6321	15, 100 or 300 µg/disc	spot test	-/- -/+	-/+	Authors reported what appeared to be total increase in colony counts rather than the presence or absence of a ring of revertant colonies.	Shiau et al., 1981
Reverse mutation	B. subtilis	TKJ5211, TKJ6321	1-300 µg/plate	liquid incubation assay	-	+ +	Incubation was for 30 minutes prior to plating.	Shiau et al., 1981
Reverse mutation	Escherichia coli	WP2tryhcr+ WP2tryhcr-	100 µg/plate	plate incorporation	NR	+ +	NC	Shirasu et al., 1976; Kada et al., 1974, 1980
Reverse mutation	E. coli	WP2hcr	5-500 µg/plate	plate incorporation	+/-	+	Responses were not reported individually for presence or absence of S-9.	Moriya et al., 1983
Reverse mutation	E. coli	WP2uvrA	<10 mg/plate	plate incorporation	+/-	+	Same as above	Waters et al., 1982
Forward mutation	mouse lymphoma cells	L51784	NR	in culture medium	+/-	+	Same as above	Waters et al., 1982
Mutation	Chinese hamster ovary cell	CHO/HGPRT	0.25-4.0 µg/ml	in culture medium	-	+	The mutation frequency increased with increased concentration of folpet. Medium contained no serum.	O'Neill et al., 1981
Recessive lethal	Drosophila melanogaster	NA	3.3 mM	feeding	NA	-	NC	Vogel and Chandler, 1974
Recessive lethal	D. melanogaster	NA	NR	feeding	NA	+	NC	Waters et al., 1982

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TABLE 5-2 (cont.)

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Mitotic gene conversion	Saccharomyces cerevisiae	D4ade2 Dtrp5	200-500 ppm	in culture medium	-	+	Dose-related increased frequency of convertants for both strains at pH 6.0. Similar effects were obtained at pH 4.5 and 3.0.	Siebert et al., 1970
Mitotic gene conversion	S. cerevisiae	ade2, trp 5	0.024 mM	in culture medium	-	+	Positive in both strains.	Fahrig, 1974
Mitotic gene conversion and recombination	S. cerevisiae	D3, D7	NR	NR	+/-	+	The effects of the activator being present or absent were not reported, but the response was positive for both strains.	Waters et al., 1982
Differential toxicity	B. subtilis	H17 Rec+ M45 Rec-	10 µg/disc	spot test	NR	+	NC	Shirasu et al., 1976; Kada et al., 1980
Differential toxicity	B. subtilis E. coli S. typhimurium	H17 Rec+ M45 Rec- W3110 (PolA+) p3478 (PolA-) uvrB, rec	NR	NR	-	+	NC	Waters et al., 1982
Unscheduled DNA synthesis	human lymphocytes	NR	5 µg/mL	in culture medium	NR	-	Folpet inhibited scheduled DNA synthesis, but had no effect on unscheduled DNA synthesis.	Rocchi et al., 1980
Unscheduled DNA synthesis	human cells	WI-38	NR	NR	+/-	-	Responses were not reported individually for presence or absence of S-9.	Waters et al., 1982
Sister chromosome exchange	Chinese hamster ovary cells	V79	0.5 or 1.0 µg/mL	in culture medium for 8 hours	NR	-	NC	Sirianni, 1978
Abnormal chromosomes	human lymphoid cells	NR	5, 10 or 15 µg/mL	in culture medium for 15 minutes	NR	+	The cells pretreated with folpet had significant increases in the number of abnormal chromosomes.	Sirianni, 1978

08/08/84 0569p

TABLE 5-2 (cont.)

Assay	Indicator Organism	Strain	Concentration or Dose	Application Method	Activation System	Response	Comments	Reference
Chromosome aberrations	human lymphocytes	Burkitt's lymphoma	2.5 µg/mℓ 5.0 µg/mℓ	in culture medium	- -	- + at 6, 12 and 18 hours	The chromosomal changes were significant at $p<0.05$. The lymphoma cells had received continuous exposure of unspecified duration. The medium contained 10% fetal calf serum. The chromosomes were analysed at 3, 6, 12, 24, 48 and 72 hours after folpet exposure.	Sirianni and Huang, 1978
	human lymphocytes	normal	0.5 µg/mℓ 1.0 µg/mℓ 2.0 µg/mℓ 4.0 µg/mℓ	in culture medium	- - - -	- + at 3 and 6 hours + at 3 and 6 hours + at 3 and 6 hours		
Dominant lethal	mice	ICR/sim	1/4 MTD 1/2 MTD MTD	ingestion in corn oil	NA	-	MTD is the maximum tolerated dose, defined as the dietary level which may produce up to 20% weight loss, mild but transient clinical signs, no inhibition of reproduction and no mortality.	Waters et al., 1982
Dominant lethal	rats	Osborne-Mendel	2.5 mg/kg/day 5.0 mg/kg/day 10.0 mg/kg/day	intraperitoneal for 5 days	NA	- - +	The increased mean early deaths/pregnancy and number of litters with one or more early deaths occurred the third week after treatment with folpet.	Collins, 1972
			50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	oral administration for 5 days	NA	- + +	The increased number of litters with two or more early deaths occurred in the second and third week after treatment with folpet.	
Cytogenic effect	mouse	Swiss albino	125-500 mg/kg	intraperitoneal	NA	+	No chromosomal differences between folpet-treated cells and controls were detected 3.6 and 24 hours after treatment.	Sirianni, 1978

NA = Not applicable; NR = not reported

The presence or absence of S-9 was not reported (Shirasu et al., 1976; Kada et al., 1980). In a yeast assay, folpet was a potent inducer of mitotic gene conversion, but no mammalian activation system was included in the experiment (Siebert et al., 1970).

In Drosophila sex-linked recessive lethal assays, folpet was described as mutagenic (Waters et al., 1980) and weakly mutagenic (Valencia, 1981). These two abstracts contained no data. After either injecting ~0.2 µl of folpet (concentrations varied between 0.2 and 1 mg/ml) into the abdomen of 4-day-old Drosophila males or continuous feeding of folpet to larvae from the first instar until adult, Kramers and Knaap (1973) found folpet not to be mutagenic in fruit flies. Similarly, after feeding adult Drosophila males a 3.3 mM solution of folpet, no increase in the number of recessive lethal mutations was observed in their offspring (Vogel and Chandler, 1974).

In a dominant lethal assay, 9- to 10-week-old rats received folpet intraperitoneally in doses of 2.5, 5.0 and 1.0 mg/kg/day for 5 days and by intubation in doses of 50, 100 and 200 mg/kg/day for 5 days (Collins, 1972). After treatment, the males were mated and the total number of implantations, early fetal deaths and late fetal deaths were recorded on day 13 of pregnancy. Statistical analysis indicated that there was a significant increase in the number of early fetal deaths in the litters 3 weeks after intraperitoneal treatment of the males. Although not statistically significant according to the methods employed in the study, increases in the numbers of early fetal deaths occurred in the litters during the first 6 weeks after oral treatment of male rats with doses of 100 and 200 mg/kg/day of folpet. A dose of 50 mg/kg/day of folpet by intubation produced a slight increase in the number of early deaths, particularly during the first 4 weeks after treatment. Oral intubation of folpet was associated with a statistically

significant increase in the percentage of litters with two or more early fetal deaths, 2 and 3 weeks after the cessation of treatment at doses of 100 and 200 mg/kg/day. A dose of 50 mg/kg/day produced an increase in the percentage of litters with two or more early fetal deaths, but the increase was not statistically significant according to the methods employed in the study. Bridges (1975) implied that a higher level of statistical significance could be obtained using analysis of variance rather than the individual paired comparison testing used originally by Collins (1972).

In another dominant lethal study at Industrial Bio-Test (IBT) Laboratories, male mice, 60-70 days old, received one intraperitoneal injection of 5 or 10 mg/kg of folpet dissolved in corn oil (Kennedy et al., 1975). After mating with untreated females, the percentage of pregnant females, as well as the number of implantation sites and the number of early fetal deaths in their offspring, was recorded. Although the percentage of pregnant females appeared lower when mated with males treated intraperitoneally with 10 mg/kg of folpet, no statistical analysis of the data was performed, and Kennedy et al. (1975) concluded that folpet was not mutagenic. The U.S. EPA (1983) has invalidated the mouse mutagenicity study performed at IBT Labs.

Negative results were obtained in a third dominant lethal assay performed by Waters et al. (1982). In this study, 20 male ICR/51M mice 3-4 months old were fed folpet for 7 weeks at the MTD or one-half or one-quarter of this dose. At the termination of treatment, the males were bred to two females. Breeding was for 7 days and was repeated weekly for 8 weeks. At mid-term in pregnancy, the females were killed and examined for early fetal deaths, late fetal deaths and live fetuses to determine if dominant lethal effects occurred. It was reported that folpet was negative in this assay; no specific details of the results were provided.

Two human lymphocyte cell lines were cultivated in RPMI No. 1640, 10% fetal calf serum and antibiotics (Sirianni and Huang, 1978). One cell line came from a normal child and was treated continuously with DMSO-dissolved folpet at doses of 0.5, 1.0, 2.0 and 4.0 µg/mℓ of culture medium. The other cell line came from a child with leukemia and was pulse-treated for 15 minutes with DMSO-dissolved folpet at doses of 2.5, 5.0, 10.0 and 15.0 µg/mℓ of culture medium. Chromosomal aberrations were noted in the normal cells 3 hours after treatment with folpet at a dose of 1.0, 2.0 and 4.0 µg/mℓ, and at 6 hours at a dose of 2.0 and 4.0 µg/mℓ. No chromosomal aberrations were present 12 and 24 hours after treatment, but cells were not dividing when treated with 4 µg of folpet/m. of culture medium. Chromosomal aberrations were noted in the leukemic cells up to 24 hours after treatment with folpet (5 µg/mℓ). Cultures receiving folpet in doses of 10 and 15 µg/mℓ did not undergo mitosis. Sirianni and Huang (1978) concluded that folpet produced a dose-dependent inhibition of cell growth and an increase of chromosomal aberrations, but did not address the inactivating effect on folpet of sulfhydryl groups contained in the fetal calf serum included in the culture medium.

Folpet produced a statistically significant, dose-dependent increase in reverse mutations in Chinese hamster ovary cells cultivated in a serum-free medium (O'Neill et al., 1981). The doses of folpet ranged from 0.1-4.0 µg/mℓ. Folpet inhibited scheduled, but not unscheduled, DNA synthesis in cultivated human lymphocytes (Rocchi et al., 1980).

5.3. TERATOGENICITY

Six pregnant New Zealand rabbits were exposed by gavage to 80 mg/kg/day of folpet on days 7-12 of gestation (Fabro et al., 1966). The day of mating was designated day zero of pregnancy. Five pregnant New Zealand rabbits

receiving no treatment constituted the negative control group; five pregnant New Zealand rabbits receiving by gavage 150 mg/kg/day of folpet on days 7-12 of gestation made up the positive control group. On day 28 of pregnancy, the does were killed and the number of live, dead and malformed fetuses, as well as the number of resportion sites, were recorded. The body weight of the offspring was determined. Folpet did not appear to affect any of these parameters as reported in this study (Fabro et al., 1966).

Groups of 2, 4, 5 and 5 pregnant hamsters were treated by gavage with 500, 400, 300 and 200 mg/kg/day of folpet, respectively, on days 6-10 of gestation (Robens, 1970). In a single exposure experiment, groups of 6-13 pregnant hamsters were treated by gavage to folpet in doses ranging from 400-1000 mg/kg in 100 mg increments on day 7 or day 8 of gestation. The control group was made up of 43 pregnant hamsters, which received no treatment; the vehicle control group, 99 pregnant hamsters, was treated with carboxymethyl cellulose (Table 5-3). On day 15 of pregnancy, the hamsters were killed with CO_2 inhalation. The number of resorption sites and the number of live and dead fetuses were recorded. The number of fetuses with malformations was noted, as well as the type of malformation. Maternal mortality occurred at the high-dose levels used in both the single and multiple exposure experiments in this study. No malformed fetuses were observed when pregnant hamsters were treated with multiple doses (200-500 mg/kg/day) of folpet. There was an increased incidence of malformed fetuses in the offspring of mothers exposed to a single dose of folpet at all levels tested except the lowest (400 mg/kg) on day 7 or 8 of pregnancy as compared with the incidence of malformed fetuses in controls. The most common malformation was exencephaly described as protrusion of neural tissue through the cranium accompanied by "severly retarded" cranial bone formation,

TABLE 5-3

Teratogenicity of Folpet[a]

Daily Dose[b] (mg/kg/day)	Days of Treatment[c]	Maternal Mortality[d]	Fetal Mortality[e]		Malformed Fetuses[f]	
500	6-10	2/2	NA		NA	
400	6-10	3/4	5/7	(71.4%)	0	
300	6-10	1/5	5/48	(10.4%)	0	
200	6-10	0/5	5/57	(8.8%)	0	
1000	7 or 8	5/8	26/32	(81.3%)	3/7	(42.9%)
900	7 or 8	3/6	2/26	(7.7%)	5/25	(20.0%)
800	7 or 8	1/10	33/99	(33.3%)	1/66	(1.5%)
700	7 or 8	1/7	6/61	(9.8%)	2/56	(3.6%)
600	7 or 8	4/13	15/84	(17.9%)	8/74	(10.8%)
500	7 or 8	0/10	23/91	(22.5%)	3/91	(3.3%)
400	7 or 8	1/9	6/93	(6.5%)	0	
0[g]	7 or 8	0/99	29/1107	(2.6%)	4/1081	(0.4%)
0	NA	0/43	66/1588	(4.1%)	7/1536	(0.4%)

[a]Source: Robens, 1970

[b]Folpet was given orally in CMC which consisted of 0.5 g sodium carboxymethyl cellulose, 0.4 g Tween 60, 0.9 g sodium chcride, 2.0 g benzyl alcohol, and water, q.s. 100 ml.

[c]The day after mating was considered day 0. All mothers and offspring were evaluated on day 15 of pregnancy.

[d]Maternal mortality indicates the number of dams who died during the experiment/total number of dams undergoing treatment.

[e]Fetal mortality indicates the total number of fetuses dying in utero, as well as the number of resorption sites/total number of implantation sites.

[f]Malformed fetuses indicates the number of fetuses with malformations/ total number of fetuses born.

[g]Vehicle control

NA = Not applicable

followed by fused ribs, shortened or curved tail and limb defects. One pup had a cranial pimple which was a localized mild case of exencephaly. There appeared to be a roughly inverse relationship between fetal mortality rate and the incidence of malformed fetuses.

McLaughlin et al. (1969) reported in an abstract that 75 or 150 mg/kg/day given in gelatin capsules to pregnant New Zealand white rabbits on days 6-16 of gestation produced no teratogenic effects in the offspring.

In an abstract of the results of a large-scale NCI study performed at Bionetics Research Laboratories (Courtney et al., 1970), folpet was reported to be teratogenic in mice. In a later abstract (Courtney et al., 1978), oral (100 mg/kg/day), subcutaneous (100 mg/kg/day) and inhalation (830 mg/hr/m^3 for 4 hours/day) exposure to folpet on days 6-13 of gestation was reported to cause no malformations in the offspring of CD-1 mice. However, a slight decrease in maternal body weight and a slight increase in fetal mortality were reported.

Kennedy et al. (1968), working at Industrial Bio-Test Laboratories (IBT), reported the effects of folpet on teratogenicity in rabbits and rats and on reproduction in rats. Nine Dutch-belted rabbits were treated with gelatin capsules containing 75 mg/kg/day of folpet on days 6-16 of gestation. Groups of 5, 5 and 7 New Zealand white rabbits were treated with gelatin capsules containing 18.75, 37.5 and 75.0 mg/kg/day, respectively, of folpet on days 6-16 of gestation. Controls consisted of 7 pregnant Dutch-belted and 10 pregnant New Zealand rabbits. The animals were killed and the offspring examined on day 29 of gestation. No effect was seen on the number of implantations or on the incidence of malformed fetuses. There was a dose-related increase in the number of resorptions reported in the New Zealand rabbits, which was correlated with a dose-related decrease in average litter size.

Ten pregnant albino rats were treated orally with 100 mg/kg/day of folpet on days 6-15 of gestation. Four pregnant albino rats were treated orally with 500 mg/kg/day of folpet on days 8-10 of gestation. The control animals were not well defined but appeared to be one group of 10 pregnant rats given the vehicle (corn oil) on days 6-15 of gestation and another group of 7 pregnant rats given the vehicle (corn oil) on days 8-10 of gestation. No further information was given. Kennedy et al. (1968) reported that folpet did not cause teratogenic effects in the offspring.

No details of the 3-generation reproductive study in albino rats fed folpet were given. However, Kennedy et al. (1968) concluded that folpet had no effect on mating ability, fertility or lactational performance.

Vondruska et al. (1971), also working at IBT, reported no effects in the offspring of stump-tailed macaques given 10, 25 or 75 mg/kg/day of folpet on days 21-34 of pregnancy. In rhesus monkeys, however, one out of four offspring whose mothers had received 25 or 75 mg/kg/day of folpet on days 21-34 of pregnancy had an extra rib. All other offspring were reported to be normal.

The U.S. EPA (1983) has recently invalidated several studies performed at IBT Laboratories, including studies on the teratogenicity of folpet in rabbits, monkeys and hamsters and of reproductive effects in rats. It appears that the Vondruska et al. (1971) and the Kennedy et al. (1968) studies are among those invalidated by the U.S. EPA (1983).

When injected into chicken eggs, folpet increases the number of malformations and the mortality rate of the developing embryos (Martin et al., 1978; Verrett et al., 1969).

5.4. OTHER REPRODUCTIVE EFFECTS

Kennedy et al. (1967, 1968) reported that up to 0.1% folpet in the diet of rats did not affect litter size, mating ability, fertility or lactational performance in their 3-generation reproductive study, but no data were published and this study appears to have been invalidated (U.S. EPA, 1983). In a Russian study, Mandzhgaladze and Vashakidze (1972) reported that rats fed threshold and subthreshold doses of folpet exhibited structural changes in the gonads, impaired gametogenesis, increased postnatal mortality, delayed sexual maturity and premature aging. No data were presented in the abstract.

5.5. SUBCHRONIC AND CHRONIC TOXICITY

In the NCI study (see Section 5.1.), 36 male and 36 female mice received folpet by gavage at a dose of 215 mg/kg/day on days 7-28 of life followed by exposure to the compound in the diet at a level of 603 ppm (Innes et al., 1969). Although the primary goal of the study was to determine the carcinogenicity of folpet, the incidence of noncancerous lesions was noted and appeared similar to controls. When folpet was administered orally, four male and three female mice developed focal pneumonia (control males 33/162, females 16/158); and two male and two female mice developed lymphatic infiltrations (control males 8/162, females 30/158).

In studies not available in the published literature, but summarized briefly by Martin and Worthing (1977), albino rats were fed folpet at dietary levels up to 10,000 ppm for 17 months. Dogs were fed 1500 mg/kg/day of folpet, 5 days/week for 17 months. No adverse effects, histopathological alterations or significant differences in tumor incidence were reported in either study.

5.6. OTHER RELEVANT INFORMATION

In vitro, folpet uncoupled oxidative phosphorylation (Nelson, 1971), irreversibly inhibited DNA polymerase (Dillwith and Lewis, 1980) and destroyed microsomal cytochrome P-450 (Ashley et al., 1982). Folpet binds to calf thymus histones at alkaline pH (~9), but not at neutral pH (Couch and Siegal, 1977). Gastric juice had no effect on the mutagenicity of folpet (DeFlora and Boido, 1980).

As mentioned in Section 4.3., folpet reacted avidly with thiol groups and appeared to be broken down quickly in the presence of sulfhydryl groups. Studies regarding the interaction of folpet with glutathione-dependent enzyme systems indicated that the reaction between folpet and glutatione predominated, thus preventing glutathione from participating in the deactivation of organophosphate and carbamate pesticides (Davidek and Seifert, 1975, 1977; Seifert and Davidek, 1975). This may have important consequences when mixtures of pesticides are used.

The acute oral LD_{50} is >10 g/kg for rats (Wiswesser, 1976) and 22.6 g/kg for albino rabbits (Martin and Worthing, 1977). The intraperitoneal LD_{50} for rats is 68 mg/kg (Ashley et al., 1982).

6. AQUATIC TOXICITY

6.1. ACUTE

The acute toxicity of folpet has been determined with 1 species of freshwater invertebrate, 10 species of freshwater fish and 2 species of marine fish (Table 6-1). Johnson and Finley (1980) reported 96-hour LC_{50} values for technical grade folpet (88-93% purity). The 96-hour LC_{50} was 2500 µg/ℓ for an amphipod species, Gammarus fasciatus, and ranged between 39 and 298 µg/ℓ for eight fish species. The geometric mean of the 96-hour LC_{50} values for these fish species was 99 µg/ℓ.

Schneider (1979) reported 96-hour LC_{50} values for two wettable powder formulations containing 50 or 75% folpet. The 96-hour LC_{50} values of the two formulations were 190 and 146 µg/ℓ, respectively, for rainbow trout, Salmo gairdneri. The 96-hour LC_{50} of the 50% formulation was 680 µg/ℓ for bluegills, Lepomis macrochirus. Comparison of these LC_{50} values with those reported by Johnson and Finley (1980) with technical grade material for the same species indicates that the wettable powder formulations are less toxic even if the LC_{50} values are corrected for percent active ingredient. The only other information concerning acute toxicity to freshwater animals was provided by Abedi and Turton (1968), who reported that 1 ppm folpet killed zebrafish larvae within 48 minutes.

Acute toxicity data are available for two species of marine fish (see Table 6-1). The 24-hour LC_{50} was 1560 µg/ℓ for white mullet and 2500 µg/ℓ for longnose killifish (Butler, 1963).

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of folpet to aquatic animals were not located in the available literature cited in the Appendix.

TABLE 6-1

Acute Toxicity of Folpet to Aquatic Organisms

Species	Concentration (µg/ℓ)	Effects	Reference
FRESHWATER			
Amphipod *Gammarus fasciatus*	2500[a]	96-hour LC_{50}	Johnson and Finley, 1980
Coho salmon *Onchorhynchus kisutch*	106[a]	96-hour LC_{50}	Johnson and Finley, 1980
Rainbow trout *Salmo gairdneri*	39[a]	96-hour LC_{50}	Johnson and Finley, 1980
Rainbow trout *Salmo gairdneri*	146[b]	96-hour LC_{50}	Schneider, 1979
Rainbow trout *Salmo gairdneri*	190[c]	96-hour LC_{50}	Schneider, 1979
Brown trout *Salmo trutta*	66[a]	96-hour LC_{50}	Johnson and Finley, 1980
Lake trout *Salvelinus namaycush*	87[a]	96-hour LC_{50}	Johnson and Finley, 1980
Fathead minnow *Pimephales promelas*	298[a]	96-hour LC_{50}	Johnson and Finley, 1980
Channel catfish *Ictalurus punctatus*	108[a]	96-hour LC_{50}	Johnson and Finley, 1980
Bluegill *Lepomis macrochirus*	72[a]	96-hour LC_{50}	Johnson and Finley, 1980
Bluegill *Lepomis macrochirus*	68[c]	96-hour LC_{50}	Johnson and Finley, 1980
Smallmouth bass *Micropterus dolomieui*	91[a]	96-hour LC_{50}	Johnson and Finley, 1980
Yellow perch *Perca flavescens*	177[a]	96-hour LC_{50}	Johnson and Finley, 1980
Zebrafish *Brachydanio danio*	1000	lethal within 48 minutes	Abedi and Turton, 1968

TABLE 6-1 (cont.)

Species	Concentration (µg/ℓ)	Effects	Reference
SEAWATER			
White mullet *Mugil cephalus*	1560	24-hour LC_{50}	Butler, 1963
Longnose killifish *Fundulus similis*	2500	24-hour LC_{50}	Butler, 1963

[a]Technical grade 88-93%

[b]Wettable powder, 75%

[c]Wettable powder, 50%

6.3. PLANT EFFECTS

The only available information concerning the effects of folpet on aquatic plants was provided by Butler (1963) who reported that exposure to 1.0 mg/ℓ for 4 hours resulted in a 31.9% decrease in productivity of natural marine phytoplankton communities.

6.4. RESIDUE

Pertinent data regarding residues of folpet in aquatic organisms were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Although residue data were not located, the calculated BCF of folpet in fish is 618 (Kenaga, 1980), indicating that this chemical has a relatively high bioconcentration potential. This BCF was calculated by Kenaga (1980) by using previously published water solubility data and regression equations. The water solubility of folpet was reported to be 1 mg/ℓ. As seen in Table 6-1, all but one of the LC_{50} values for freshwater animals were <1 mg/ℓ. The LC_{50} values for freshwater amphipods and the two marine fish species were >1 mg/ℓ. These results indicate that folpet is acutely toxic to most freshwater species at concentrations well below its solubility limit. Additional marine species must be tested before any conclusions can be reached concerning the toxicity of folpet to marine species at realistic dissolved concentrations in seawater.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Tolerances for folpet in or on raw agricultural products have been established by the U.S. EPA (Code of Federal Regulations, 1979). These tolerances range from 15-50 ppm for fruits and vegetables depending on the particular item.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of folpet were not located in the available literature.

8. RISK ASSESSMENT

The NCI study (Innes et al., 1969), in which two strains of mice were administered 215 mg/kg/day of folpet by intubation from days 7-28 of age followed by 603 ppm of folpet in the diet through ~18 months of age, reported that the incidence of cancer was no higher in the treated than in the control animals. McCann and Ames (1976) pointed out that folpet may have been inactivated by the vehicle, which was gelatin, in the initial 21 days of gavage administration in the 1969 study. In addition, the number of mice exposed to folpet for 18 months is small and the number of mice in the control group with cancer seems high.

From mutagenicity studies, it appears that folpet is mutagenic in the absence of serum, blood or S-9 mixture (Moriya et al., 1978; Shiau et al., 1981), but it has a very short half-life when in contact with proteins, especially those that contain sulfhydryl groups. It is unfortunate that so few mutagenicity experiments took into account the instability of folpet in the presence of thiol groups. Folpet was found to be less mutagenic in the presence of S-9 when tested within the parameters of the same experiment (Shiau et al., 1981). In dominant lethal studies, an i.p. injection (10 mg/kg/day for 5 days) of folpet (LOAEL) caused a statistically significant increase in the mean early deaths/litter in the third week after male rats were treated (Collins, 1972). Doses of 2.5 and 5.0 mg/kg/day for 5 days produced no statistically significant effect (NOEL); however, oral intubation at 50, 100 and 200 mg/kg/day for 5 days (all the levels tested) produced a statistically significant increase in the percentage of litters with two or more early deaths (Collins, 1972). The effect did not appear to be linearly related to the dose.

Because of its structural similarity to thalidomide, the teratogenicity of folpet has been extensively studied, but the results are not clear. Folpet appears to produce malformations in chickens, but its effects in mammals are equivocal. In hamsters (Robens, 1970) and mice (Courtney et al., 1978), resorption rate or fetal mortality (or both) were increased when the mothers were exposed to folpet. The analysis of resorption rates in hamsters was complicated by increased maternal and fetal mortality (Robens, 1970). The teratogenicity studies and three-generation reproductive study performed at IBT Laboratories (Kennedy et al., 1967, 1968; Vondruska et al., 1971) appear to have been invalidated (U.S. EPA, 1983). The NCI study in mice reported by Innes et al. (1969) and chronic studies in dogs and rats summarized by Martin and Worthing (1977) do not provide sufficient detail with which to determine an ADI.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this chapter.

The CBI Appendix to this document reviews other animal data that indicate that folpet is carcinogenic to mice. A q_1^* for humans of 4.97×10^{-3} $(mg/kg/day)^{-1}$ is recommended for use in estimating the increased risk of cancer to humans from folpet exposure. The q_1^* was calculated from the dose-response data for duodenal neoplasias in male mice fed folpet in the diet using the linearized multistage model developed by Kenneth Crump and

adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of this q_1^* value for humans (assuming 70 kg bw) from animal data is the cube root of the body weight ratio (Federal Register, 1980).

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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